INTERIM GUIDANCE ON THE USE OF ANTIVIRAL AGENTS FOR TREATMENT OF HUMAN INFECTIONS WITH AVIAN INFLUENZA A (H7N9)

This interim guidance provides recommendations for antiviral treatment of confirmed cases, probable cases, and patient under investigation (PUI) of human infection with avian influenza A(H7N9) virus. This guidance will be updated as additional information on H7N9 virus transmissibility, epidemiology, and antiviral susceptibility patterns becomes available.

These interim recommendations are based upon current information and the following considerations:

- Current lack of a vaccine for H7N9 virus
- Severe H7N9 disease with substantial mortality to date
- Limited current human-to-human H7N9 virus transmission but potential for increased transmission in the future

Clinicians should consider the possibility of avian influenza A(H7N9) virus infection in persons presenting with acute febrile respiratory illness and an appropriate recent travel or exposure history (see Interim Guidance on Case Definitions for Novel Influenza A (H7N9) Case Investigations).

Randomized controlled trials of currently approved influenza antivirals have demonstrated decreased time to symptom improvement when used to treat otherwise healthy persons with acute uncomplicated influenza caused by circulating seasonal influenza strains within the first few days of illness.

On the basis of these trials and additional pooled analyses and observational studies, many experts believe that when antiviral agents are given early in the course of uncomplicated influenza illness, both the duration of symptoms and the likelihood of complications are reduced. Clinical benefit is greatest when antiviral treatment is administered early, especially within 48 hours of influenza illness onset. Among patients hospitalized with seasonal influenza A (including 2009 H1N1) or B, or avian influenza A(H5N1) virus infections, observational studies suggest that early treatment reduces disease severity and mortality.

Although earlier antiviral treatment results in greater clinical benefit, observational studies support the use of antiviral treatment in hospitalized patients even when started after 48 hours of illness.

While no data are available regarding early neuraminidase inhibitor treatment of persons infected with H7N9 virus, laboratory testing with functional assays indicates that H7N9 viruses are susceptible to neuraminidase inhibitors (oseltamivir and zanamivir), but resistant to adamantanes (amantadine and rimantadine). Therefore, amantadine and rimantadine are not recommended for treatment of H7N9 virus infection.

INFLUENZA ANTIVIRAL TREATMENT RECOMMENDATIONS

- **Because of the potential severity of illness associated with H7N9 virus infection, it is recommended that all confirmed cases, probable cases, patient under investigation (PUI) with moderate/severe ILI illness and patient under investigation (PUI) with mild ILI illness and co-morbidities** (see Interim Guidance on Case Definitions for Novel Influenza A (H7N9) Case Investigations) **receive antiviral treatment with a neuraminidase inhibitor as early as possible. Treatment should be initiated even if it is more than 48 hours after onset of illness.**

- **Laboratory testing and initiation of antiviral treatment should occur simultaneously;** treatment should not be delayed for laboratory confirmation of influenza or H7N9 infection.

- Oseltamivir is recommended for treatment of persons of any age; zanamivir is recommended for children aged 7 and older. Clinicians may refer to the manufacturer's package inserts for additional information regarding dosing, contraindications, and potential adverse events.

UNCOMPLICATED ILLNESS IN OUTPATIENTS

- Given the anticipated lack of preexisting immunity to H7N9 viruses, the potential for rapid progression, severe disease, and fatal outcomes with H7N9 infection, and low adverse event profile of neuraminidase inhibitors, **treatment with oseltamivir or inhaled zanamivir should be initiated when confirmed cases, probable cases, patient under investigation (PUI) with moderate/severe ILI illness and patient under investigation (PUI) with mild ILI illness and co-morbidities are recognized, even if more than 48 hours from illness onset and even for apparently uncomplicated illness**.

    - **Antiviral treatment is recommended as soon as possible especially for those considered to be at increased risk of complications associated with influenza** such as children aged <2 years, adults aged ≥65 years, pregnant women, and persons with certain underlying medical conditions.

    - **For outpatients with no high risk co-morbidities and with uncomplicated disease in whom fever is absent and symptoms are nearly resolved, decisions to initiate antiviral treatment should be based on clinical judgment.** Persons who are not treated with antiviral medications should be monitored for progression of illness.

    - Inhaled zanamivir is not recommended for persons with underlying airway disease (e.g., asthma or chronic obstructive pulmonary disease).

- **Recommended duration of treatment for uncomplicated illness is 5 days.**

HOSPITALIZED PATIENTS

- **Initiation of antiviral treatment is recommended as early as possible for hospitalized patients, even if more than 48 hours from illness onset.**

- **For hospitalized patients and patients with severe or complicated illness, treatment with oral oseltamivir (and not inhaled zanamivir) is recommended** because of the lack of data for inhaled zanamivir in patients with severe influenza illness.

- **The optimal duration and dose of therapy are uncertain in severe or complicated influenza. Pending further data, longer courses of treatment (e.g., 10 days of treatment) should be considered for severely ill hospitalized H7N9 patients.**

    - Clinical judgment and virologic testing of lower respiratory tract specimens by rRT-PCR should guide decisions to consider treatment regimens longer than 5 days for patients with severe and prolonged illness. For these patients, lower respiratory tract specimens, such as bronchoalveolar lavage or endotracheal aspirate, are preferred; an nasopharyngeal aspirate/swab, throat swab and nasal swab may be collected if lower respiratory specimens are not available.

    - Longer treatment regimens might be necessary in immunosuppressed persons who may have prolonged viral replication and also are at risk of developing antiviral-resistant virus.

    - A higher dose of oseltamivir has been recommended by some experts (e.g., 150 mg twice daily in adults with normal renal function) for treatment of influenza in immunocompromised patients and in severely ill hospitalized patients .